

STATE-OF-THE-ART PAPER

Percutaneous Transcatheter Aortic Valve Implantation: Assessing Results, Judging Outcomes, and Planning Trials

The Interventionalist Perspective

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Aortic valve stenosis is increasing in frequency as the population ages. Surgical aortic valve replacement is the gold standard for symptomatic patients with severe aortic valve stenosis. However, in a subset of high-risk patients, the surgical option is excluded due to severe comorbidities. Recently, an alternative to surgical aortic valve replacement—percutaneous aortic valve replacement (PAVR)—has emerged. Since the first PAVR in a human in 2002, the percutaneous heart valves (PHVs) have already undergone several modifications from first generation devices. Currently, there are 2 PHVs in clinical application, a balloon-expandable and a self-expandable PHV, with several others achieving first-in-man application. With the extremely rapid technological advancements, PAVR is probably here to stay. The next steps required would be to formulate goals to assess results and outcomes of PAVR, and plan trials to test their clinical applicability. This article discusses how best to assess results and outcomes, which may require a paradigm shift in mindset. Apart from the randomized controlled trial, some of the more novel concepts in trial design, which may be more suitable in this area, are also explored. (J Am Coll Cardiol Intv 2008;1:341–50) © 2008 by the American College of Cardiology Foundation

The prevalence of aortic valve stenosis (AS) increases with advancing age, and is present in 4.6% of adults ≥ 75 years of age (1). With increasing life expectancy and an aging population, the number of patients with AS will greatly increase (2). Once symptoms occur, the prognosis is poor (3). Surgical aortic valve replacement (AVR), with an operative mortality of 3% to 8%, is the treatment of choice for the majority of these patients, with relief of symptoms and improved survival (4,5).

However, in a significant percentage of patients, mainly the very elderly and those with severe comorbidities, the risk of AVR is often considered to be much higher, and these patients are, there-

fore, not offered surgery (4–8). Balloon aortic valvuloplasty has a role in providing temporary relief of symptoms (9,10), although the recurrence rates are unacceptably high, with a 1-year survival rate of only 54% to 75% (11–13). Its main role is palliation or as a bridge to surgical AVR. Medical therapy for these patients is associated with a dismal outcome (14). Because of the limited therapeutic options in this subset of patients, there has been interest in the development of a less invasive AVR strategy.

Recently, an alternative to surgical AVR—percutaneous aortic valve replacement (PAVR)—has emerged. This was first demonstrated by Andersen et al. (15) in 1992, who delivered a porcine bioprosthesis attached to a wire-based stent at various aortic sites with satisfactory hemodynamic results. Subsequently, other investigators were able to perform catheter delivery

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of bioprosthetic valves of various designs in animals (16-18).

The first human percutaneous valve replacement was performed by Bonhoeffer et al. (19) in 2000, where a percutaneous heart valve (PHV) made from bovine jugular vein mounted on a platinum-iridium stent was successfully placed in a stenotic right ventricle to pulmonary conduit with good results.

Two years later, Cribier et al. (20) reported the first successful PAVR. Various groups have now reported their early experiences with the balloon-expandable and self-expandable PHVs (21-28). With the intense interest of the interventional cardiology community, technological advancements are being made exponentially. PAVR is probably here to stay, and highly likely a matter of time before it becomes an effective option for

selected patients with severe symptomatic AS and severe comorbidities. The next goal is to plan trials, to assess the results, and define clinical applications for PAVR, assuming these trials are favorable.

Abbreviations and Acronyms

AS = aortic valve stenosis

AVR = aortic valve replacement

CABG = coronary artery bypass graft

FDA = Food and Drug Administration

LV = left ventricle/ventricular

OPC = Objective Performance Criteria

PAVR = percutaneous aortic valve replacement

PHV = percutaneous heart valve

QOL = quality of life

RCT = randomized controlled trial

STS = Society of Thoracic Surgeons

Current Status of Aortic PHVs

Currently, there are 2 PHVs in clinical trials, the balloon-expandable Cribier-Edwards (Edwards Lifesciences Inc., Irvine, California) valve and, more recently, the Edwards-Sapien valve (Edwards Lifesciences Inc.), and the self-expandable CoreValve (CoreValve, Irvine, California). The balloon-expandable PHV consists of 3 pericardial leaflets initially

equine (Cribier-Edwards), and currently bovine (Edwards-Sapien), mounted within a tubular, slotted, stainless steel balloon-expandable stent (Fig. 1). Current generation devices require either a 22-F or 24-F sheath for delivery (20,21,25,27,28). This PHV was initially implanted via the antegrade transseptal approach. There were several problems with this approach (21,24,28), and the retrograde approach has since been shown to be safer with the use of a proprietary steerable delivery catheter. Because of the large delivery system utilized, surgical repair of the vascular access site is required (25,27). There are currently on-going randomized controlled trials (RCTs) using this PHV (PARTNER [Placement of AoRTic traNscathETer] US and PARTNER EU trials).

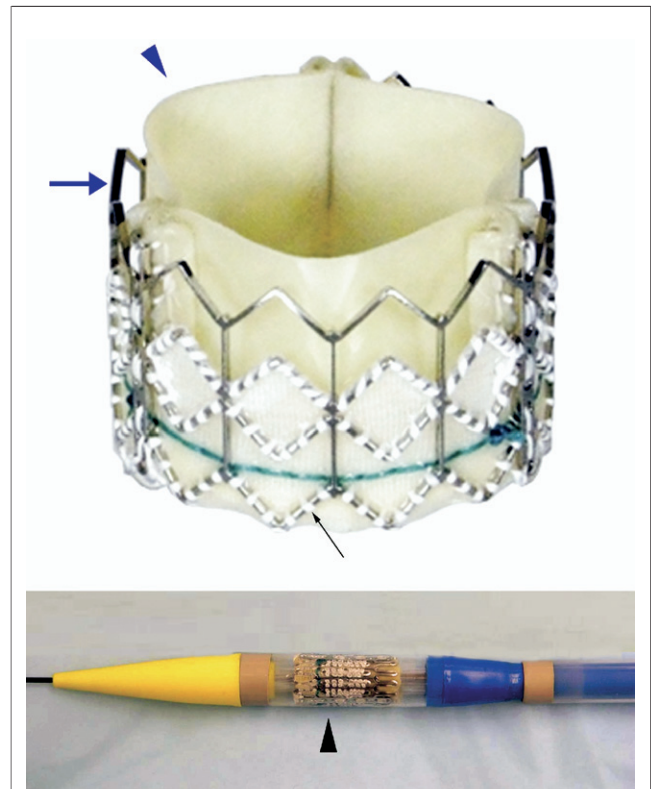


Figure 1. Edwards-Sapien PHV

(Top) Bovine pericardium leaflets (blue arrowhead) sutured (expanded polytetrafluoroethylene) (black arrow) onto a stainless steel stent frame (blue arrow). (Bottom) Delivery catheter (Retroflex II, Edwards Lifesciences Inc., Irvine, California) with valve loaded (black arrowhead). PHV = percutaneous heart valve.

The self-expandable PHV (CoreValve) consists of 3 pericardial tissue leaflets, initially bovine and currently porcine, mounted and sutured in a self-expandable nitinol stent (Fig. 2). The stent frame is 50 mm, with the lower (inlet) portion having a high radial force to expand and exclude the calcified aortic leaflets; the middle portion carries the valve—the coaptation point of the leaflets is actually supra-annular—and is constrained to avoid obstructing the coronary arteries; and the upper portion (outlet) is flared to fixate the stent in the ascending aorta and provide longitudinal stability. Early generation devices required 25-F sheaths; later devices incorporated porcine pericardial tissue constrained within 21-F, and now 18-F sheaths (22,23,26). This PHV is implanted via the retrograde approach.

There are several other aortic PHVs that have already done the first-in-man application, such as the Paniagua PHV of Endoluminal Technology Research (Miami, Florida) (Fig. 3) (29), the Enable PHV of ATS (Minneapolis, Minnesota) (3-F) (Fig. 4), the AorTx PHV of Hansen Medical (Mountain View, California) (Fig. 5), the Direct

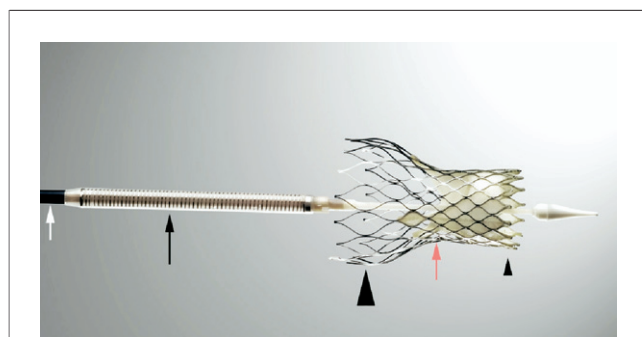


Figure 2. CoreValve PHV

A 12-F delivery catheter shaft (**white arrow**), 18-F delivery case, which contains valve (**black arrow**) with a flexible distal nose cone; opened valve consisting of the lower (inlet) portion (**small arrowhead**), the constrained middle portion to allow coronary perfusion (**red arrow**), and the upper (outlet) portion (**large arrowhead**). PHV = percutaneous heart valve.

Flow PHV of Direct Flow Medical (Santa Rosa, California) (Fig. 6), the Lotus PHV from Sadra Medical (Campbell, California) (Fig. 7), the Perceval PHV from Sorin Group (Arvada, Colorado) (Fig. 8), and the Jena PHV from JenaValve Technology (Wilmington, Delaware) (Fig. 9) (Table 1). Furthermore, several other innovative devices are currently in the developmental stage or in pre-clinical testing (30,31).

Target Patient Population

As with any medical procedure, the risk/benefit ratio of aortic PHV implantation must be carefully considered. The benefits provided by this novel procedure must be weighed eventually against what is considered today the “gold standard”—surgical AVR. Bearing in mind, however, the excellent track record of surgical AVR, it seems prudent to initially target those patients who are at high surgical risk due to severe comorbidities. Thus, the patients currently enrolled in these studies are chosen based on a risk score, such as the EuroSCORE or Society of Thoracic Surgeons (STS) score (32,33). The other set of patients who may be considered at present are those with a deteriorated aortic bioprosthesis and deemed at high risk for surgical reoperation, and this “valve-in-valve” concept has already been reported (34). With technological advancements, it is expected that the ease of implantation will improve and complications will decrease. In order to consider lower risk and younger patients as candidates for this new technology, additional long-term durability data will be required before advocating this procedure as a possible substitute to surgical AVR.

Therefore, the target population will rapidly evolve, with the speed of evolution depending on proven risk/benefit ratio derived from ongoing clinical trials. The complications experienced with this new technology reflect the steep

learning curve combined with the fact that these were early device designs (21,22,25–28), and with increased follow-up, other problems may emerge. Ideally, prospective data should be gathered serially from well-characterized populations, to validate the selection criteria for this procedure. These will evolve rapidly once the durability of the PHV is comparable to the surgically implanted valve and as the safety of implanting PHVs surpasses that of surgical techniques.

Assessing Results

Assessing results should primarily focus on the implantation procedure and the immediate performance of the PHV. The criteria used to assess the results of surgical AVR should be applied to all PHVs. Newly implanted prostheses will require consistently accurate implantation in the correct anatomical position with relative ease. They should not obstruct the coronary ostia, and remain in situ without dislodgement or embolization. Of critical importance is the hemodynamic performance of the PHVs. The residual gradient should not be greater than currently accepted for surgical valve prostheses, with an acceptable effective valve orifice area. In addition, there should not be significant transvalvular regurgitation, and there should be a tight seal between the native structures and the device to minimize

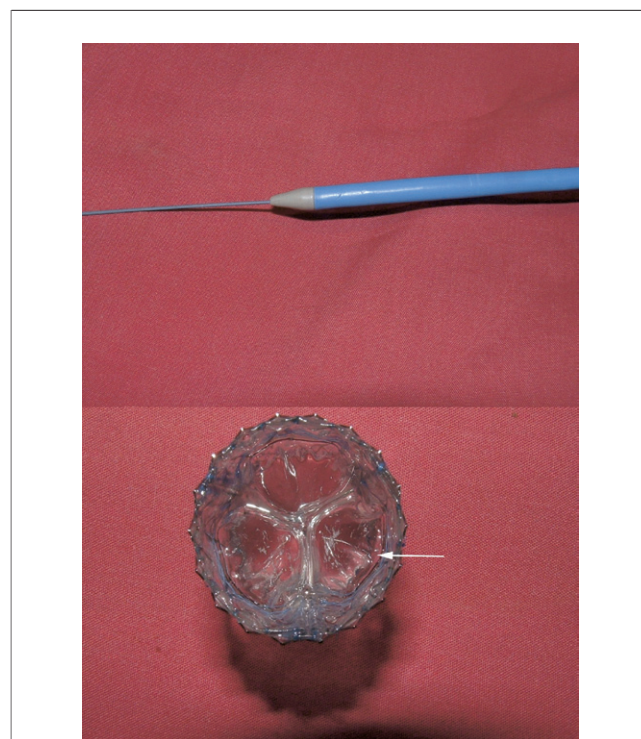


Figure 3. Paniagua PHV

(Top) Delivery catheter, which houses the balloon, stent, and valve. (Bottom) Proprietary processing of bovine pericardium with a valve leaflet thickness of 40 μ m (**arrow**). PHV = percutaneous heart valve.

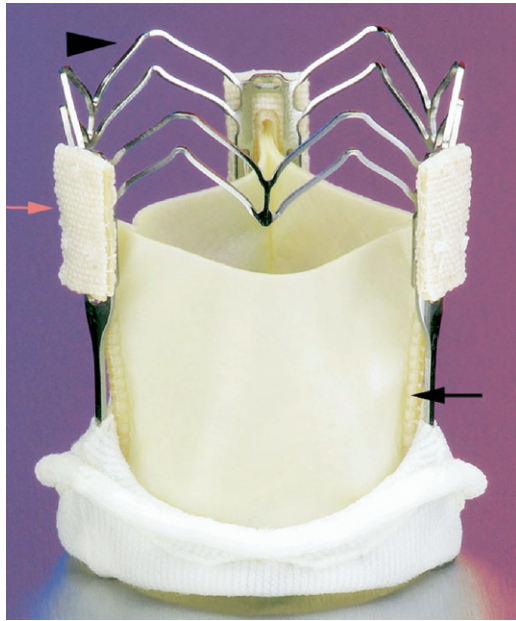


Figure 4. Enable PHV

Pericardial valve leaflets (**black arrow**) sutured onto a self-expandable nitinol frame (**arrowhead**) with pledgets providing support and fixation (**red arrow**). PHV = percutaneous heart valve.

paravalvular leaks. Valve function, hemodynamics, regurgitation, and paravalvular leaks are best assessed by echocardiography since it can be easily and repeatedly performed and interpreted by the same observer. Criteria for differentiating between transvalvular regurgitation from paravalvular leak and assessing their severity using echocardiography have been well defined previously (35).

Judging Outcomes

Outcomes should be assessed from 2 different perspectives—the objective outcomes after PHV implantation, and the subjective component of quality-of-life (QOL) parameters.

Objective outcomes. PERIPROCEDURAL OUTCOME. This encompasses in-hospital and 30-day outcomes, which are the main end points used in surgical AVR reports. Mortality and all major adverse cardiovascular, cerebral, and vascular events should be recorded and compared. In addition, device failure or device-related complication such as infection, hemolysis, and thrombocytopenia (22), should also be classified under major adverse events. Furthermore, careful attention should be made to ensure that there is no evidence of prosthesis-patient mismatch, as prosthesis-patient mismatch, defined as an indexed effective orifice valve area $<0.8 \text{ cm}^2/\text{m}^2$, is an independent predictor of cardiac events, 30-day and long-term mortality in patients undergoing surgical AVR (36–38).

SHORT-TERM (UP TO 1 YEAR) OUTCOME. This is usually taken to begin after 30 days up until 1 year after implant. The PHV position and function should be assessed, as well as left ventricular (LV) function and other hemodynamic indexes that reflect performance of the PHV. Echocardiography is the imaging modality of choice today, since serial measurements can be made easily and inexpensively, although it can be subjective with interobserver variability (39,40). Regional and global LV systolic function assessed by tissue Doppler imaging have been shown to improve immediately after PHV placement (41). Echocardiography, however, may not be sufficiently accurate to account for prostheses migration, and, therefore, other imaging technologies such as computed tomographic angiography may be required.

Early experiences revealed that paravalvular leaks were not infrequent after aortic PHV implantation, although significant leaks were uncommon (0%, 7%, and 15% incidence of paravalvular leaks \geq grade 3+) (26–28). Paravalvular leaks were also common after surgical AVR, being present in 47% of patients in one study. However, 97% of

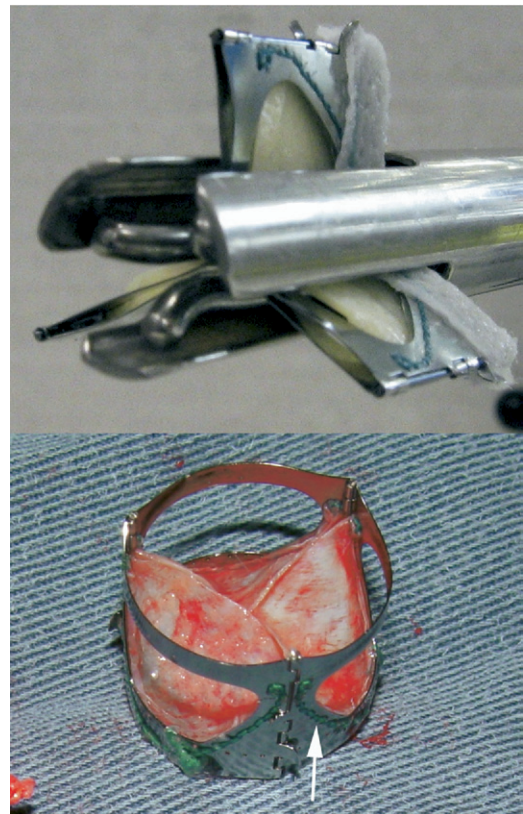


Figure 5. AorTx PHV

(**Top**) Delivery catheter with the valve crimped within. (**Bottom**) Pericardial leaflets sutured (**arrow**) onto a self-expandable nitinol stent. PHV = percutaneous heart valve.

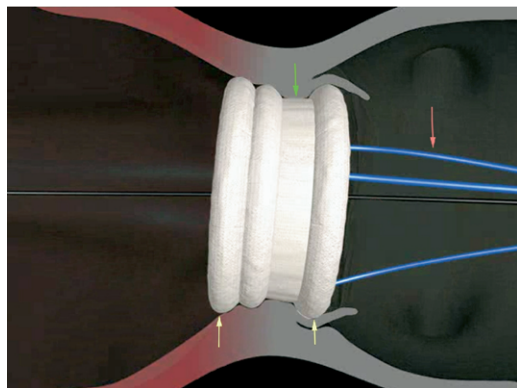


Figure 6. Direct Flow PHV

The valve is constructed of 2 hydrophilic coated inflatable rings (**yellow arrows**) with bovine pericardial tissue sutured in a noninflatable cylindrical segment that anchors the aortic annulus (**green arrow**). The valve is controlled with 3 control wires (**blue**) and is fixed in position by using a permanent polymer to inflate the 2 inflatable rings. PHV = percutaneous heart valve.

these were mild or moderate, and did not change in severity or affect LV indices over 5 years (35). Clinically, the patient should be assessed for symptom improvement by changes in New York Heart Association functional class, vascular access site problems, and for other adverse events as defined earlier in the text.

LONG-TERM (>1 YEAR) OUTCOME. In addition to the continuing follow-up of the parameters previously discussed, the long-term durability of the PHV needs to be established. The long-term results may not be so crucial currently as patients are at very high risk with expected high mortality rates. However, with time, this procedure may become suitable for those at lower risk, and survival duration will take on greater prominence. The current regulatory bench testing requirements for surgically implanted aortic prostheses may not be sufficient to predict durability or stability of these PHVs, given the immense number of covariates that may play a role. Valve migration is conceivable due to continuous mechanical movement of the LV outflow tract and remodeling of the surrounding tissues (42). This concern theoretically may possibly be reduced with the self-expandable PHV models due to their ability to adapt geometrically if the conformation and the structure of the surrounding tissues change over time (42). It is unclear, however, whether the self-expandable PHV models would lead to a higher incidence of late aortic erosion and possible rupture (42). Furthermore, the long-term durability of these stents under complex motion conditions will need to be proven as there already are reports of valve stent fractures in the pulmonary position (43), which resulted in symptom recurrence or stent embolization.

SUBJECTIVE OUTCOMES. In our zest to judge outcomes, it is imperative that we do not constrain ourselves to assess tangible data, morbidity, and longevity but, more importantly, also focus on QOL. It should not be forgotten that the primary aim of any medical therapy is to make patients feel better. Therefore, concise QOL parameters must be assessed. There are several QOL questionnaires available, and it is beyond the scope of this article to determine which methodology is most ideal (44). Although more subjective, QOL may be more important to the patient than the

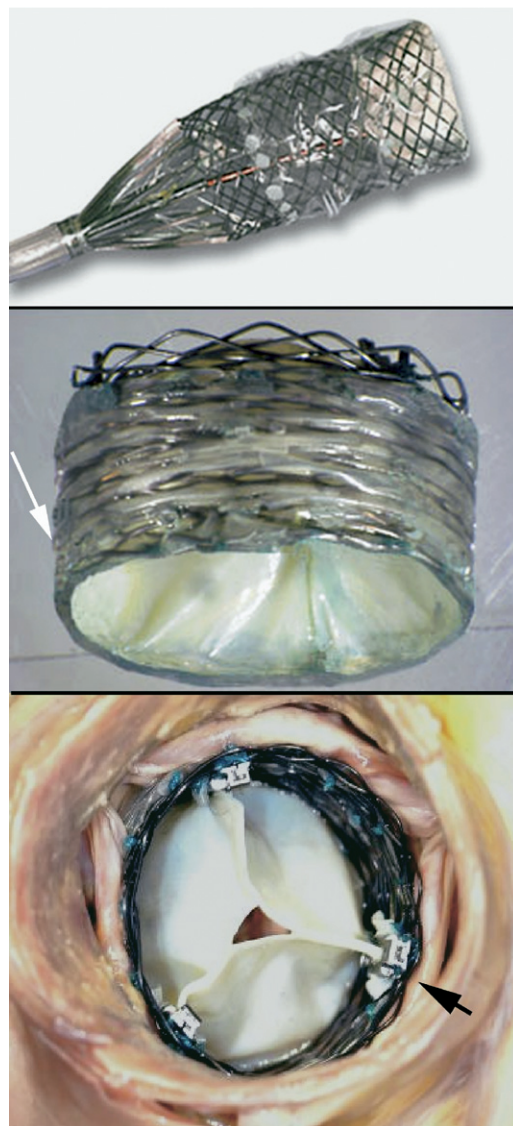


Figure 7. Lotus PHV

(**Top**) Nitinol valve unsheathed but still attached to delivery catheter. (**Middle**) Valve after shortening with increase in radial strength; sealing membrane of the valve (**white arrow**). (**Bottom**) Valve viewed from the aortic surface with the locks seen (**black arrow**). PHV = percutaneous heart valve.

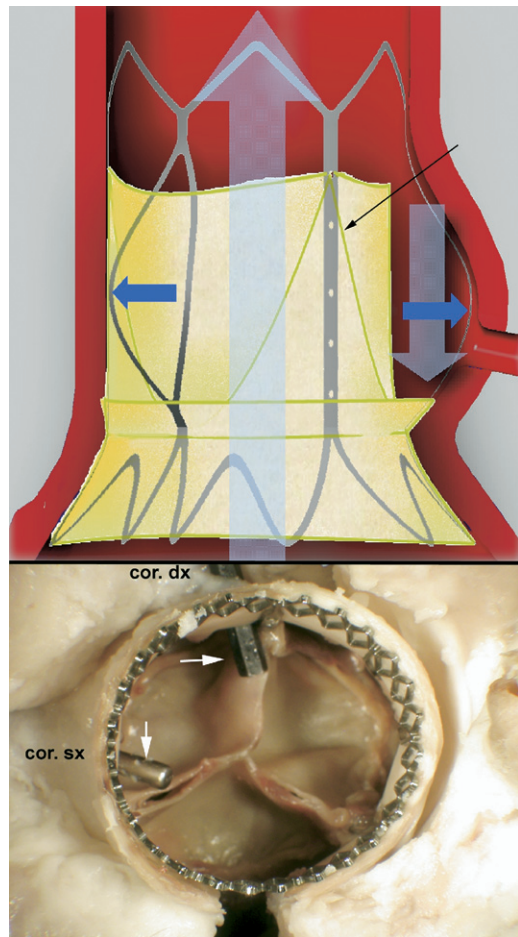


Figure 8. Perceval PHV

(Top) Self-expandable proprietary stent that approximates the shape of the aortic root and sinuses (blue arrows), and the nonexpandable posts (black arrow) that support the pericardial tissue valve. It has a double pericardial sheet that enhances sealing against the native valve (large down-pointing purple/grey arrow) to decrease paravalvular leaks. Note: Large vertical up-pointing arrow signifies direction of blood flow. (Bottom) Valve viewed from the aortic surface with probes through patent coronary ostia (white arrows). cor. = coronaria; dx = dextra (right coronary artery); PHV = percutaneous heart valve; sx = sinistra (left coronary artery).

objective indices of mortality and morbidity. This is particularly so if the treatment goal is to improve symptoms, and if physiologic measures that correlate with a patient's experience are unavailable or inadequate. There is a tendency to assume a robust link between physiologic measurements and a patient's functional status and well-being, but unfortunately these often prove misleading. Patients with similar hemodynamic AS profiles can have vastly different symptom severity (45). Furthermore, changes in conventional measures of clinical status may only show weak or modest correlation with changes in QOL (46). Strict focus on physiologic measures may lead the physician to believe that

the treatment is beneficial, when, in fact, it does not change the way patients feel.

Because these early trials enrolled patients with very high surgical risk or those who were nonsurgical candidates, outcomes must be stratified by condition severity with some of the risk scores mentioned previously (e.g., logistic EuroSCORE or STS score) (32,33,47-49). Any increment in survival and, perhaps more importantly, improvement in QOL would be meaningful for this high-risk population.

The outcomes of these trials should be compared not only with the current surgical AVR results, but also the transapical route of implanting PHVs (50,51), and other innovative surgical techniques such as implantation of an apico-aortic conduit (52). We must keep in mind that most surgical alternatives are, however, not required to be scrutinized by any regulatory agency for safety and efficacy, and, therefore, any anecdotal data derived from these reports may be difficult to compare.

Approval Process and Clinical Validation

The approval process and clinical validation involve pre-clinical testing consisting of device concept, in vitro testing and then in vivo (animal) testing. The new PHVs will require Failure Mode Effects and Criticality Analysis, and risk/benefit relevant to the particular device. Once these have been established, the device will then be subjected to clinical validation.

Prosthetic heart valves have been implanted in the U.S. since the 1960s, and *none* have required RCTs by the Food and Drug Administration (FDA) for approval. The FDA

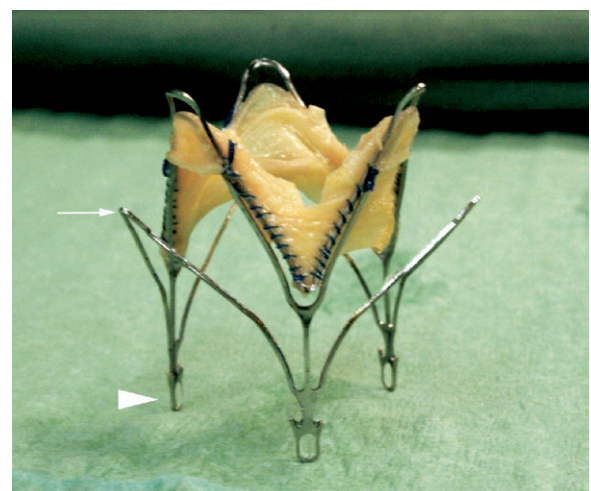


Figure 9. JenaValve PHV

A low-profile, repositionable, nitinol, self-expandable stent with pericardial leaflets. The upper portion (arrow) is flared to fixate and orient the valve in the aortic sinus; the eyelets (arrowhead) secure the valve for delivery.

Table 1. Percutaneous Heart Valve Technologies

| Device | Company | Expansion Mechanism | Valve Material | Stent Material | FIM | Clinical Trials |
|-------------|-----------------------------------|--|----------------|-----------------------------|------|-----------------|
| Sapien | Edwards | Balloon-expandable | Pericardium | Stainless steel | 2002 | Yes |
| CoreValve | CoreValve | Self-expandable | Pericardium | Nitinol | 2004 | Yes |
| Paniagua | Endoluminal Technologies Research | Balloon-expandable and self-expandable | Pericardium | Stainless steel and nitinol | 2003 | No |
| Enable | ATS (3-F) | Self-expandable | Pericardium | Nitinol | 2005 | No |
| AorTx | Hansen Medical | Self-expandable | Pericardium | Nitinol | 2006 | No |
| Direct Flow | Direct Flow Medical | Polymer-injected | Pericardium | Polymer | 2006 | No |
| Lotus | Sadra Medical | Self-expandable | Pericardium | Nitinol | 2007 | No |
| Perceval | Sorin Group | Self-expandable | Pericardium | Nitinol | 2007 | No |
| JenaValve | JenaValve Technology | Self-expandable | Pericardium | Nitinol | 2007 | No |

FIM = first-in-man.

instead relies on an Objective Performance Criteria (OPC) developed through analysis of historical data (53,54) that was facilitated by a standardized set of definitions of complications published by the American Association of Thoracic Surgeons and the STS in 1987/1988. A requirement, however, for using simple OPC rates (percent per year) to summarize a complication is that its risk is constant across time. Therefore, if a complication is time related, this constant risk assumption does not hold (55). For example, length of follow-up would be critical in assessing structural failure of tissue heart valves (12 to 15 years?). Also, the OPC method depends on identifying all valve-related complications, including those that cause death, so a high autopsy percentage must be a pivotal requirement of the study. Because there are no OPCs for these events (mortality and sudden death), it is important that fatal valve-related events be classified into the OPC category to which they belong (55). For these reasons, the OPC approach may not be appropriate for all medical devices, and will not work for PHVs since the risk of structural failure is *not* constant across time.

Designing Trials

For PAVR to become a viable alternative, the procedural and long-term outcomes must be better than medically treated patients and not inferior to surgical AVR in patients with comparable risk scores.

There are now 6 published case series of patients undergoing PAVR (21,22,25–28). Both the results of the balloon- and self-expandable PHVs have been reported. A total of 181 patients have been studied (22,26–28). Patient selection was similar in all series. All patients had severe symptomatic AS, and were refused surgery after evaluation by both the surgeon and cardiologist. In the 3 most recent series, PHV implantation was successful in 146 of 171 (85%) patients, with a mean 30-day mortality of 13.5% (23 of 171 patients), compared with a predicted mortality of >20% (26–28). In those patients who had successful implantation, there was dramatic hemodynamic and clinical

improvement, with early and midterm relief of heart failure. Although clinical stability was observed up to 24 months (27,28), assessment of long-term durability will require at least 5 years of follow-up. From these data, it can be seen that currently only the highest-risk patients for conventional surgical AVR have been studied.

To conduct trials assessing PAVR, the patient population has to be rigorously defined. In this respect, the risk scores as mentioned earlier have an important role in stratifying patients (33,48,49). The European studies tend to use the logistic EuroSCORE (32). This uses the same risk factors as the additive EuroSCORE, but is more accurate for predicting mortality in combined coronary artery bypass graft (CABG) and valve surgery (56), and for individual risk prediction in the very high risk, since the additive EuroSCORE tends to underestimate risk in this group (32,48,49). The U.S. studies conversely tend to use the STS score (33), although all current publications on PAVR used the logistic EuroSCORE (22,25–28). The STS score was developed using data for isolated CABG surgery only, whereas the EuroSCORE database included 30% valve operations. Both scores were validated during their development (33,48,49), and both were subsequently validated for isolated valve replacement (7,47,57). The EuroSCORE has better accuracy in predicting perioperative mortality after CABG compared with the STS score, and is also superior to many other score systems (58–60). Recently, however, it was shown that, for isolated surgical AVR in very high-risk patients, the STS score most accurately predicted perioperative and long-term mortality when compared with both the logistic and additive EuroSCOREs, as well as the newer Ambler score developed and validated on patients undergoing heart valve surgery (61,62).

Next, the correct risk/benefit ratio based on a balance between safety and effectiveness perceived for the reduction in surgical risk and superiority over medical therapy will need to be established. And with the advent of the transapical route of aortic PHV, PAVR must also now be shown to be superior or, at least, equivalent to this technique. The end

points must be appropriate and should include device function and durability, clinical efficacy (functional status and QOL), morbidity, and mortality.

Based on the encouraging early results of PAVR, RCTs using a balloon-expandable PHV comparing percutaneous aortic PHV implantation with surgical AVR or medical therapy are underway (PARTNER-US and PARTNER-EU). The FDA requires that the new PHVs be proven noninferior to surgical AVR and superior to medical therapy through an RCT. A position statement by 4 professional societies involved with PAVR also recommended RCTs to evaluate this new technology (63). Randomizing patients with severe symptomatic AS to medical therapy raises certain ethical issues since prognosis with this modality is dismal, with 50% mortality at 2 years (14,45). Achieving clinical equipoise with surgical AVR can also be problematic as it pits a new and evolving technology with a steep learning curve against a mature technique. Demonstrating superiority can require a large sample size when small treatment benefits are anticipated. This is particularly pertinent as the proportion of patients with severe symptomatic AS at high surgical risk would be small. Using composite end points can decrease sample size requirement, albeit at the risk of limiting the subanalysis of individual components since events may not be of equal magnitude (e.g., death vs. reoperation) (64). Utilizing noninferiority design with an appropriate delta will also reduce sample size, but it may confound the ability to determine true equivalence.

Several newer concepts in trial design, which have been approved for Investigational Device Exemption trials of other cardiovascular devices that permit more timely study completion and expedite availability of innovative devices, have to be considered (65). Prospective adaptive trial designs allow for modifications to some aspects (e.g., sample size) of the trial without penalty to the statistical analysis. Another innovative method, the Bayesian trial design, can provide an advantage over the traditional and more often used frequentist model if certain conditions exist (65). Frequentist methods draw conclusions by relying only on data produced in a given study whereas Bayesian methods integrate available prior information (55). The Bayesian approach is, therefore, less rigid, obviates the need for fixed sample sizes and one-time assessments, and is most useful in clinical studies where information is collected in an ongoing process, and where repeated interim analyses are required. Prior distribution of the parameter(s) of interest, however, must be quantified (66). Despite this limitation, the Bayesian approach may facilitate analysis of a study of smaller size and/or shorter duration. This approach has been used for approval of prosthetic cardiac valves (e.g., analyzing thromboembolic event rates using information derived from older prosthetic valves) and may prove helpful for evaluating PHVs (65,66).

For non-RCTs, the use of a propensity score analysis may allow more appropriate comparison of control to treatment data (65,67). This addresses imbalances between groups by incorporating confounders and other covariates into a model predicting the probability of assignment to a particular treatment. It can be used for adjustment or for matching patients who have similar probabilities of receiving a therapy. Differences in outcomes between treated and untreated patients with equal propensity scores provide a less biased estimate of therapy effect.

Post-Marketing Surveillance

As the long-term function and durability of devices may not be reliably extrapolated from the relatively short period of a pre-market study, monitoring the performance after marketing approval is a valuable approach (68). Post-market studies can provide evidence for the safety and effectiveness of a device, when it is used in the 'real world' rather than in trials of healthcare provision. However, it is imperative that such studies meet acceptable standards. Many devices receive approval from the FDA on condition that post-market registries are performed (69). This should be taken one step further with aortic PHVs, and compulsory registries should be mandated for these new technologies. If not instigated early, a valuable opportunity to obtain rigorous long-term durability and outcome data in the 'real-world' environment will be lost.

Conclusions

Ever since the first human aortic PHV implant, the field has progressed extremely rapidly. This is a critical period in its evolution, and whether PAVR would one day not only be a therapeutic option in the normal risk cohort but become the next "gold standard" remains to be seen. The road is long and arduous, but the journey has begun.

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Key Words: aortic valve stenosis ■ surgery ■ percutaneous ■ bioprosthesis ■ clinical trials ■ heart valve prosthesis implantation.